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THE ROLE OF MICROBIOTA IN INFLAMMATION

Ktsoyan Z.A.[1], Ghazaryan K.A.[1], Khachatryan Z.A.[1], Manukyan G.P.[1], Sedrakyan A.M.[1], Arakelova K.A.[1], Gevorgyan Z.U.[2], Mnatsakanyan A.A.[2], Boyajyan A.S.[1], Hakobyan G.S.[3], Beloborodova N.V.[4], Olenin A.Yu.[4], Osipov G.A.[5], Kelly D.[6], Grant G.[6], Coutts A.[6], Flint H.[6], Aminov R.I.[7]

[1]Institute of Molecular Biology of National Academy of Sciences of RA, Yerevan, Republic of Armenia
[2]"Nork" Clinical Hospital of Infectious Diseases, Ministry of Health of Republic of Armenia, Yerevan, Republic of Armenia
[3] "Armenia" Republican Medical Center, Yerevan, Republic of Armenia
[4]Research Institute of General Reanimatology, Russian Academy of Medical Sciences, Moscow, Russian Federation
[5] Scientific Center of Cardiovascular Surgery, Russian Academy of Medical Sciences, Moscow, Russian Federation
[6] University of Aberdeen, Rowett Institute of Nutrition and Health, Aberdeen, United Kingdom
[7] Technical University of Denmark, National Veterinary Institute, Kongens Lyngby, Denmark
rustam.aminov@gmail.com

Inflammation is an integral part of the normal innate immunity processes in response to physical damage, chemical agents, and pathogens. In recent years, however, there has been a very substantial increase in the rate of chronic diseases with the inflammatory component such as allergy, asthma, rheumatoid arthritis, chronic periodontitis, ulcerative colitis and Crohn's disease, chronic sinusitis, and many other conditions. While the molecular mechanisms governing the acute inflammation response against various pathogens are largely well understood, the mechanisms that trigger and sustain chronic inflammation in the apparent absence of a defined pathogen are not entirely clear.

In our comparative study we investigated different types of inflammation in patients with: (i) auto-inflammatory condition, familial Mediterranean fever, (ii) auto-immune condition, systemic lupus erythematosus, (iii) peptic ulcer caused by *Helicobacter pylori* infection,

and (iv) salmonellosis caused by infection with two serotypes of *Salmonella enterica, S.* Typhimurium and *S.* Enteritidis.

We found that the profiles of inflammation mediators in each case are highly specific and correspond to a particular disease. Investigation of the microbiota in some diseases demonstrated that there are specific changes in the microbiota composition as well. Moreover, these microbiota alterations are accompanied by the shifts in microbial products and metabolites entering systemic circulation in different diseases. Our results suggest that the healthy state is characterised by the intricate balance between the host and its microbiota resulting in a controlled inflammation. Once this balance is compromised, due to internal or external factors, the inflammation may get out of control and become a self-sustainable process.

ADIPOGENESIS INHIBITION BY DERMONECROTIC TOXINS: DIFFERENTIAL REGULATION OF NOTCH1, PREF1/DLK1, AND B-CATENIN SIGNALLING

Aminova L.R.

Department of Microbiology,
University of Illinois at Urbana-Champaign, USA
laminova@zuchem.com

The dermonecrotic toxins from *Pasteurellamultocida* (PMT), *Bordetella* (DNT), *Escherichia coli* (CNF1-3), and *Yersinia* (CNFY) modulate their G-protein targets through deamidation and/or transglutamination of the Gln residue in the active site. This results in activation of the G protein and its cognate downstream signalling pathways. Whereas DNT and the CNFs act on small Rho GTPases, PMT acts on the α subunit of heterotrimeric G(q), G(i), and G(12/13) proteins.

Our results demonstrated that PMT potently blocks adipogenesis and adipocyte differentiation in a calcineurin-independent manner through the downregulation of Notch1 and stabilization of β-catenin and Pref1/Dlk1, the key proteins in signalling pathways strongly linked to cell fate decisions, including fat and bone development. The Rho/ROCK inhibitor Y-27632 prevented or reversed these toxin-mediated effects, strongly